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PTO/SB/33 (07-05)

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PRE-APPEAL BRIEF REQUEST FOR REVIEW		Docket Number: 19459-006US1
CERTIFICATE OF MAILING BY EXPRESS MAIL Express Mail Label No. <u>EV 744 620 038 US</u> <u>SEPTEMBER 5, 2006</u> Date of Deposit	Application Number 09/830,693	Filed January 29, 2002
	First Named Inventor Shiau et al.	
	Art Unit 1631	Examiner Nashaat T. Nashed
Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request. This request is being filed with a Notice of Appeal. The review is requested for the reason(s) stated on the attached sheet(s). Note: No more than five (5) pages may be provided. I am the <input type="checkbox"/> applicant/inventor. <input type="checkbox"/> assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96) <input checked="" type="checkbox"/> attorney or agent of record <u>56,637</u> (Reg. No.) <input type="checkbox"/> attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____ NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below'. <input checked="" type="checkbox"/> Total of 1 forms are submitted.		

Signature

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Typed or printed name

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Telephone number

September 5, 2006

Date



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Shiau et al. Art Unit : 1631
Serial No. : 09/830,693 Examiner : Nashaat T. Nashed
Filed : January 29, 2002 Confirmation No. : 9894
Title : COMPLEXES OF ESTROGEN α RECEPTOR BOUND TO AGONIST AND
COACTIVATOR MOLECULES (as amended)

Mail Stop: AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**STATEMENT OF REASONS IN CONNECTION WITH
PRE-APPEAL BRIEF REQUEST FOR REVIEW**

Dear Sir:

Please consider the instant remarks in connection with the Pre-Appeal Brief Request for Review ("Request") filed on even date herewith.

Background to Request and Disposition of the Application

Claims 1-25, 29-35, and 39-44, 46, 49-137, 139-142, 144-148, 150, 153, and 155 are pending in the instant application. Claims 1-25, 29-35, 39-43, 49, 51-135, 140, and 141 are withdrawn from consideration.

Claims 44, 46, 50, 136, 137, 139, 142, 144-148, 150, 153, and 155 stand rejected under one or more grounds. The various grounds of rejection articulated by the Examiner in his first action on the merits, dated December 9, 2004 (the "First Office Action"), have been reiterated in his second action on the merits, dated August 15, 2005 (the "Second Office Action"), and also in the Final Office Action, dated May 5, 2006 (the "Final Office Action"). Applicants believe that there is clear error in each of the Examiner's thrice-issued rejections and, in support of the accompanying request for a pre-appeal brief request for review, Applicants hereby point out the following errors in the rejections of record.

The Rejections of Record and Reasons for Clear Error Therein

Objections to Sequence-identifiers

In the First Office Action, the Examiner objected to Applicants' specification, alleging non-compliance with sequence labeling rules (First Office Action at page 3). In Applicants' Amendment and Response dated March 9, 2005 ("First Response"), Applicants amended the specification to insert various sequence-identifiers (SEQ ID NOs).

In the Second Office Action, the Examiner alleged that Applicant "has failed to perfect his compliance". In a response dated February 15, 2006 ("Second Response"),

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Applicants amended the specification further to introduce sequence identifiers at various positions, consistent with what Applicants understood to be the Examiner's request.

In the Final Office Action, the Examiner has objected to use of ranges of sequence identifiers in connection with a single complex, and has suggested that the presence of different sequences, referred to by the same name, is inconsistent. The Examiner's comments do not take into account Applicants' description of the subject matter in their Second Response (page 44, line 5 – page 45, line 11), which Applicants now reiterate herewith. In short, a complex as claimed includes both a protein fragment and a coactivator peptide bound thereto, each of which is represented by a different and separate sequence. Thus, at least two sequences are associated with a given complex. Furthermore, a given complex may crystallize as a dimer (*i.e.*, the smallest unit has two instances of protein and two instances of coactivator), and, the structures of each unit may not have been equivalently resolved and thus be different in their representation in the sequence listing. Therefore, each structure represented in the appendices has several sequence identifiers associated with it, and those sequences are not necessarily identical with the sequence of the protein or peptide prior to crystallization (which is identified by a different sequence identifier), solely because the coordinates in the crystal are incomplete. None of the foregoing is internally contradictory. Neither would it be confusing to one of ordinary skill in the art.

Rejections under the written description requirement of 35 U.S.C. § 112(¶1)

With regard to claims 44, 46, 50, 142, 144-147, 150, and 155, drawn to cocrystals, the essence of the Examiner's rejection is that "Applicants have provided only a single representative species ... and that the specification fails to describe ... any identifying structural characteristics or properties other than their composition." (First Office Action at page 4). Applicants responded by showing that the specification is replete with descriptions of identifying characteristics of each component (receptor, agonist, and coactivator), as well as the manner in which the components contact one another. (First Response, pages 31-33).

In Applicants' Second Response to this rejection as maintained, claim 44 was amended to recite a cocrystal bound to an agonist selected from a list, and a coactivator peptide which is either GRIP1 or is a fragment of GRIP1 having an NR-box amino acid sequence. As such claim 44, now pending, recites a significantly narrower genus of cocrystals than recited in claim 44 as originally filed. The Examiner's rejection, as stated in the Final Office Action (pages 3 – 4) does not take these amendments into account.

In particular, Applicants disagree with the Examiner's grounds for at least the following reasons. First, the Examiner dismisses Applicants' description of the various components of a cocrystal as claimed, and their *manner of interaction with one another*

because “the claims are not directed [to a] component of [a] crystal.” (Final Office Action, page 3, last para.) The smallest independent units in the crystal are complexes and as such are described by both a description of the components of each complex and the manner in which those components interact with one another. Applicants have provided such a description. Second, the Examiner states that “crystals are described by their crystal forms, symmetry element present in the crystal, and the angles between the crystal axes” (Final Office Action, page 3, last para.). Applicants respectfully point out that the pending claims do not recite parameters such as space group, and unit cell dimensions. There has never been any requirement that claims to crystals recite such parameters, just as there has never been any requirement for a claim to a liquid to recite an intrinsic property such as its viscosity. Such a requirement would not only be unduly limiting but is not required by law. Furthermore, since the Examiner has identified no crystals in the prior art having Applicants’ *composition*, Applicants have no need to distinguish their claimed crystals over others in the art based on intrinsic properties such as their crystalline parameters. Does the Examiner suggest that one of ordinary skill in the art following Applicants’ described methods, with Applicants’ disclosed materials, would arrive at crystals with different crystalline parameters from those reported by Applicants? Even if true, such an assertion is irrelevant to the interpretation that one of ordinary skill in the art has of the claims as pending. Finally, the Examiner references alleged unpredictability of protein crystallization, as a basis for alleged insufficiency of written description. Applicants believe that this too is clear error, and suggest that such arguments are more appropriately positioned with respect to rejections under alleged lack of enablement.

Regarding claims 136, 137, 139, 148, and 153, drawn to an isolated and purified complex of an estrogen receptor ligand binding domain, an agonist, and a coactivator, and various embodiments thereof, the Examiner alleges that since such claims read on “all possible [such] purified and isolated composition[s] ... in solution, vapor, amorphous precipitate, or crystalline form” and that since such claims read on crystalline forms, the foregoing grounds for rejection are valid. Applicants again disagree. First, the rejection, as reiterated in the Final Office Action does not take into account Applicants’ amendments to claims 136, and 139 which recite specific coactivators and ligands. Accordingly, the breadth alleged by the Examiner is not as great as he supposes. Furthermore, Applicants have never understood the Office to articulate the position that a claim to composition of matter was lacking a proper description because all possible phases of such a composition were not described. Thus, the fact that the claims may read on crystalline forms (that have been objected to for other reasons) cannot render them invalid, *per se*, since the claims merely recite a complex, and a complex has been clearly described in the specification. Applicants

are unaware that the Office has ever required – or now requires – Applicants to support composition of matter claims, of the type routinely examined by the Office, with a description of all phases of the materials in question. The Examiner again argues that “transforming a protein or its complexes to a crystal in specific space group and unite [*sic*] cell dimensions is not [within the capability of one of ordinary skill in the art]” (Final Office Action, page 4, first para.). Again, Applicants have never suggested, and nor do the claims require, obtaining a crystal having a *specific* space group or unit cell parameters.

Rejections under the enablement requirement of 35 U.S.C. § 112(¶1)

The Examiner has rejected claims 44, 46, 50, 136, 137, 139, 142, 144-148, 150, 153, and 155, as allegedly “failing to comply with the enablement requirement.” (First Office Action at pages 5-6.) In the Final Office Action, this rejection is reiterated, again without seeming to take into consideration Applicants’ amendments to claims 44, 136, and 139.

The essence of the Examiner’s contention is that the amount of experimentation required to practice Applicants’ claimed invention is “undue”, in particular with respect to the exact crystallization conditions. First, Applicants point out that it is clear error to argue that uncertainties in experimental conditions required for *crystallization* are pertinent to isolation and purification of complexes recited in claims 136, 137, 139, 148, and 153.

Second, Applicants point out that the Examiner’s allegations are both rebutted by Applicants’ claim amendments, and the case law. Thus, the Examiner’s assertion that the field is empirical (Final Office Action, page 5, 2nd para.) and that the experimentation involved would be undue invokes legal authority that holds otherwise: “the fact that experimentation may be complex, ..., does not necessarily make it undue, if the art typically engages in such experimentation.” *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, at 1174 (ITC, 1983). Thus, it follows that those skilled in the art would appreciate how to practice Applicants’ claimed invention, notwithstanding the fact that experimentation in that art is frequently complex.

Finally, the Examiner’s rejections under both the enablement and written description requirements of 35 USC § 112 (first paragraph) take no account of the varying scope of Applicants’ claims and are phrased as if only to consider the limitations of independent claims 44 and 136 even though they reject all claims under consideration. Nowhere has the written description support of the limitations of the claims depending from claims 44 and 136, or the enablement of such claims, been separately addressed. Applicants respectfully submit that the rejections of record cannot apply with equal force to all claims without some clearly articulated reasoning why claims of successively narrowing scope are not enabled.

Therefore, on this basis, Applicants assert that there is clear error in the rejections at least as they apply to claims 46, 50, 137, 139, and 142, 144 – 148, 150, 153, and 155.

Applicants also regret the Examiner's choice of words "confusing by design" particularly because Applicants took the trouble to explain the various materials (Second Response, at pages 44 – 45).

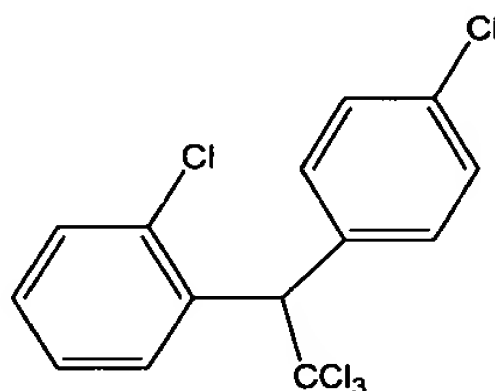
Rejections of alleged indefiniteness 35 U.S.C. § 112(¶2)

The Examiner has objected to various terms in the claims. Applicants believe that there is clear error in the Examiner's reasoning in each case, for the following reasons:

The term "estrogen receptor α binding domain" in claim 44 is objected to, yet the Examiner adopts an interpretation (Final Office Action, page 6 at (a)) consistent with Applicants' own definition (see, *e.g.*, Second Response, at page 38). This interpretation is hardly indefinite and would be perfectly understandable by one of ordinary skill in the art.

Regarding the term "GRIP1", the Examiner objects to the phrase "e.g. SEQ ID NO: 4". Since the word "e.g." is found in neither the specification nor the claims, Applicants believe that this rejection is in error. Indeed Applicants have provided evidence of the use of the term "GRIP" and its meaning in the art (First Response), and have amended claims referring to such a term to recite a corresponding SEQ ID NO (Second Response).

In respect of the term "o,p-DDT", the Examiner has suggested that Applicants are withholding the structure. To the contrary, Applicants have merely asserted that it is known to one of ordinary skill in the art. It is, in fact, as the Examiner suggests related to DDT, and has the following structure:



No fee, other than the Notice of Appeal fee is believed owing with this response. Should the Commissioner determine otherwise, he is authorized to apply any charges or credits to Deposit Account No. 06-1050 (ref. 19459-006US1).

Respectfully submitted,

Date: September 5, 2006

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